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PATENT
Atty Docket No.: SYN-0036

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Applicants: Pavel SLANINA et al. Confirm. No.: 7713
Serial No.: 10/705,926 Art Unit: 1624
Filed: November 13, 2003 Examiner: Susanna Moore
For: PROCESS FOR MAKING RISPERIDONE
AND INTERMEDIATES THEREFOR

DECLARATION UNDER 37 C.F.R. § 1.132

I, Martin Dobsik, do hereby declare as follows:

1. I am employed as a research scientist by Synthon sro., having a principal place of business at Krizikova 70, Brno, Czech Republic.
2. I received a university degree in chemistry from the Faculty of Chemistry, Technical University in Brno, Czech Republic
3. I have practiced in the field of preparative organic chemistry for five years, and currently my work focuses on projects involving the synthesis of pharmaceutically-active compounds.
4. I was asked to repeat the part of Example 1 of EP 196,132, which reads as follows:

A mixture of 12 parts of (2,4-difluorophenyl)(4-piperidinyl)-methanone hydrochloride, 12 parts of hydroxylamine hydrochloride and 120 parts of ethanol was stirred at room temperature and 10.5 parts of N,N-diethylethanamine were added. The whole was stirred and 25 refluxed for 3 hours. After cooling, the precipitated product was filtered off and dried, yielding 11 parts (100%) of (2,4-difluorophenyl)(4-piperidinyl)methanone, oxime (intermediate 3).

Application No.: 10/705,926

5. I repeated the above-cited part of Example 1 on standard laboratory glass equipment. All starting materials were commercially available. I interpreted the word "parts" to mean "weight parts." Because the actual weight in grams was not described in Example 1, I used 2 grams as the charge of "12 parts" of the starting ketone hydrochloride. I calculated the charges of the other materials based on this actual weight and according to the relative proportions given in Example 1.

6. I used the reaction conditions described in Example 1. The details of the cooling step (performed before filtration of the product), however, was not described in Example 1. Accordingly, I cooled the reaction mixture to ambient temperature (about 20°C) before the filtration step, and I filtered the mixture at ambient temperature.

7. I repeated Example 1 two times (hereafter "Experiment 1" and "Experiment 2," respectively) using the same charge, the same equipment, and the same reaction conditions. The yield of the solid product in Experiment 1 was 1.45 grams, and the yield of the solid product in Experiment 2 was 1.41 grams.

8. I expected that the oxime may have formed as a mixture of isomers differing in conformation on the =N-OH moiety, particularly the (E)-(2,4-difluorophenyl)(4-piperidinyl)methanone oxime (hereafter "the (E)-isomer") and the (Z)-(2,4-difluorophenyl)(4-piperidinyl)methanone oxime (hereafter "the (Z)-isomer"). Accordingly, I instructed my colleagues at Synthon sro. to analyze the reaction product not only with respect to the oxime product, but also with respect to the relative content of the individual isomers thereof.

9. My colleagues analyzed the content of the (E)-isomer and the (Z)-isomer using an HPLC method developed at Synthon sro. The HPLC method separated the (E)-isomer, the (Z)-

SEP 04 2007

Application No.: 10/705,926

isomer, and the ketone and enabled us to calculate the content of these three compounds.

Reference materials of the ketone hydrochloride, the (E)-isomer, and the (Z)-isomer of analytically-acceptable quality were within the possession of Synthon sro., so the identification of HPLC peaks corresponding to the above compounds was unambiguous.

10. Three samples were analyzed per my instructions, hereafter referred to as "Sample A," Sample B," and "Sample C," respectively. Sample A refers to the reaction mixture after termination of reflux heating, but before cooling and filtration. The reaction mixture was a suspension of a solid in a liquid, and I sampled the stirred mixture using an injection valve (which may have affected the homogeneity of the sampled mixture). Sample B refers to the solid product obtained by filtration. Sample C refers to the mother liquor after filtration of the solid product.

11. The results of the HPLC analyses, expressed as relative percentages of the HPLC peak intensities for the analyzed compounds, are shown in the following table.

	(E)-isomer	(Z)-isomer	Starting Ketone
Sample A – Reaction Mixture			
Experiment 1	40.33%	53.12%	0.93%
Experiment 2	33.28%	61.38%	2.70%
Sample B – Solid Product			
Experiment 1	3.33%	93.75%	2.49%
Experiment 2	1.16%	96.19%	2.65%
Sample C – Mother Liquor			
Experiment 1	72.85%	19.81%	0%
Experiment 2	74.79%	18.71%	0%

Other peaks were present, which might be attributed to side products, but the exact nature thereof was not investigated.

Application No.: 10/705,926

12. Additionally, I instructed my colleagues to analyze the chlorine content in the solid product of Experiment 2.

13. The analysis was performed by argentometric titration, which revealed that the content of chlorine in the solid product from the Experiment 2 is 14.83%, which is slightly above 1 molar equivalent of HCl with respect to the oxime.

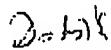
14. Based on the chlorine analysis, I conclude that the oxime isolated from the reaction mixture is in fact an oxime hydrochloride (as a mixture of the isomers (E)-oxime hydrochloride and (Z)-oxime hydrochloride). Specifically, I believe that the oxime hydrochloride is present in the reaction mixture and in the mother liquor because the basic center able to bind the HCl both in the ketone and in the oxime is distant from the reaction center, and because nowhere within the reaction course is the molar content of bases higher than the content of HCl.

15. My conclusions based on the results of argentometric titration (the chlorine analysis) were also supported by the subsequent conversion of the solid product (the oxime hydrochloride) to the free base by neutralization with an aqueous NaOH. The solid product obtained after filtration and drying was HPLC identical with the oxime, had a negligible content of HCl, and was obtained with an expected yield close to 100% conversion (1.21 grams out of the 1.45 grams of the starting oxime hydrochloride).

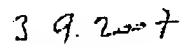
16. Contrary to the teaching of EP 196,132, the yields of my experiments were in no case 11 parts of the solid product when starting with 12 parts of the ketone hydrochloride. Our yields were only 8.7 parts and 8.46 parts, respectively, wherein 2 grams corresponds to 12 parts.

Application No.: 10/705,926

17. I hereby declare that all statements made herein of my own knowledge are true and that all statements based on information and belief are believed to be true and further that these statements have been made with the knowledge that willful false statements and the like so made are punishable by fine, imprisonment, or both under section 1001 of Title 18 of the United States Code and that such false statements may jeopardize the validity of the application or any patent issuing thereon.



Martin Dobsik



Date